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Site-Selective C−H Alkylation of Piperazine Substrates via Organic Photoredox Catalysis

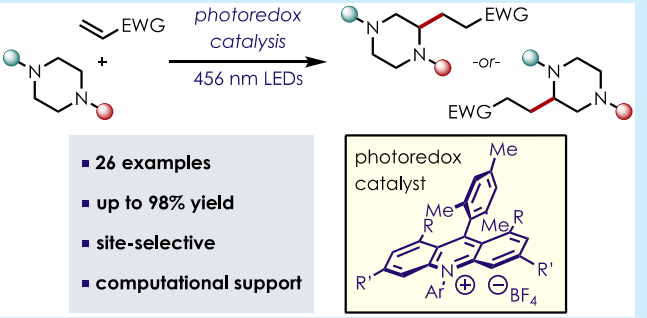
Joshua B. McManus,[†] Nicholas P. R. Onuska,[†] Matthew S. Jeffreys,[‡] Nicole C. Goodwin,[‡] and David A. Nicewicz*[,†]

[†]Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

[‡]GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, Pennsylvania 19426, United States

Supporting Information

ABSTRACT: Piperazine-containing compounds serve as one of the most important classes of compounds throughout all fields of chemistry. Alas, current synthetic methods have fallen short of providing a general method for the synthesis of highly decorated piperazine fragments. Herein, we present a site-selective approach to the C−H functionalization of existing piperazine compounds using photoredox catalysis. This manifold relies on the predictable differentiation of electronically distinct nitrogen centers within the piperazine framework, granting access to novel C-alkylated variants of the starting piperazines.



In an effort to optimize "drug-like" physicochemical properties, medicinal chemists often turn to nitrogen-containing heterocycles as integral core structures. Piperazines, containing two differentiable nitrogens and an unsubstituted, saturated carbon skeleton, were found to be the third-most prevalent such heterocycle in current pharmaceuticals behind only piperidines and pyridines (Figure 1).[1] Despite the ubiquity of piperazine-containing therapeutics, structural diversity of these compounds along the piperazine's carbon framework is remarkably limited.[1] This observation provokes the query of whether structurally diverse piperazines represent a class of inconsequential compounds or whether current synthetic limitations are hindering access to these more elaborate targets.

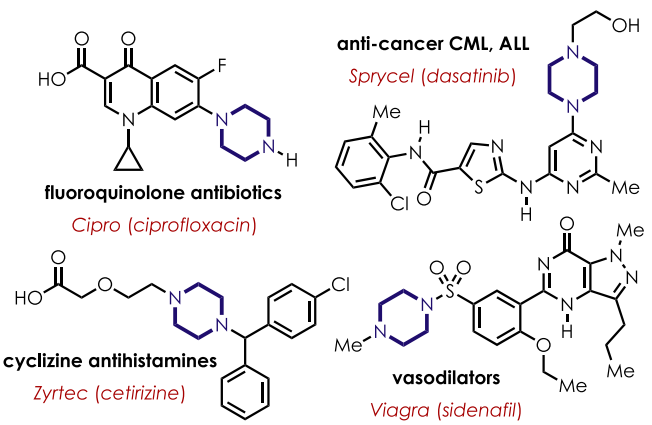


Figure 1. Representative piperazine-containing pharmaceuticals.

To date, the development of a general method for the construction of C-substituted piperazine cores has yet to be achieved. Classically, these compounds are synthesized via the reduction of 2,5-diketopiperazines generated via peptide cyclodimerizations or by the multicomponent Ugi reaction.[2−4] However, these methods require tedious multistep procedures that can offer only a subset of the desired substituted piperazines. Other methods developed for accessing substituted piperazine or morpholine-type products have traditionally relied on *de novo* syntheses of the target heterocycle via innovative cyclization strategies.[5−10]

While current methods for functionalizing existing piperazines typically rely on harsh or substrate-specific reaction conditions,[11−13] recent findings by our laboratory (Figure 2A) focusing on the alkylation of photoredox-generated α-carbamyl radicals (**1**) to give elaborate, protected secondary amine products (**2**) served as inspiration for the development of a targeted approach to the mild, site-selective, and atom-economical synthesis of substituted piperazine compounds from their more readily available unsubstituted precursors (Figure 2B).[14] A single example has been disclosed using this type of strategy in a photoredox setting;[15] however, we believe expanding on such a strategy would grant direct access to a variety of piperazines bearing additional functionality from inexpensive but structurally related starting materials. This approach would be advantageous from a medicinal chemistry

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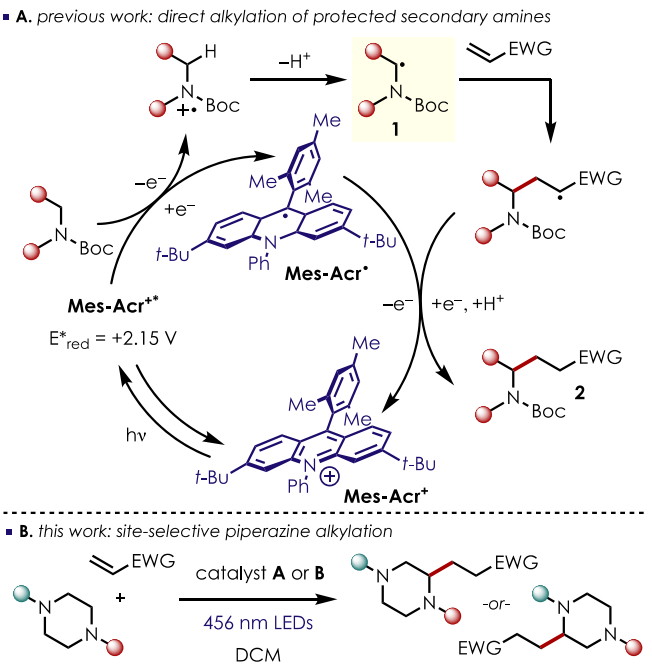


Figure 2. (A) Mechanism for the alkylation of carbamates and (B) site-selective piperazine alkylation.

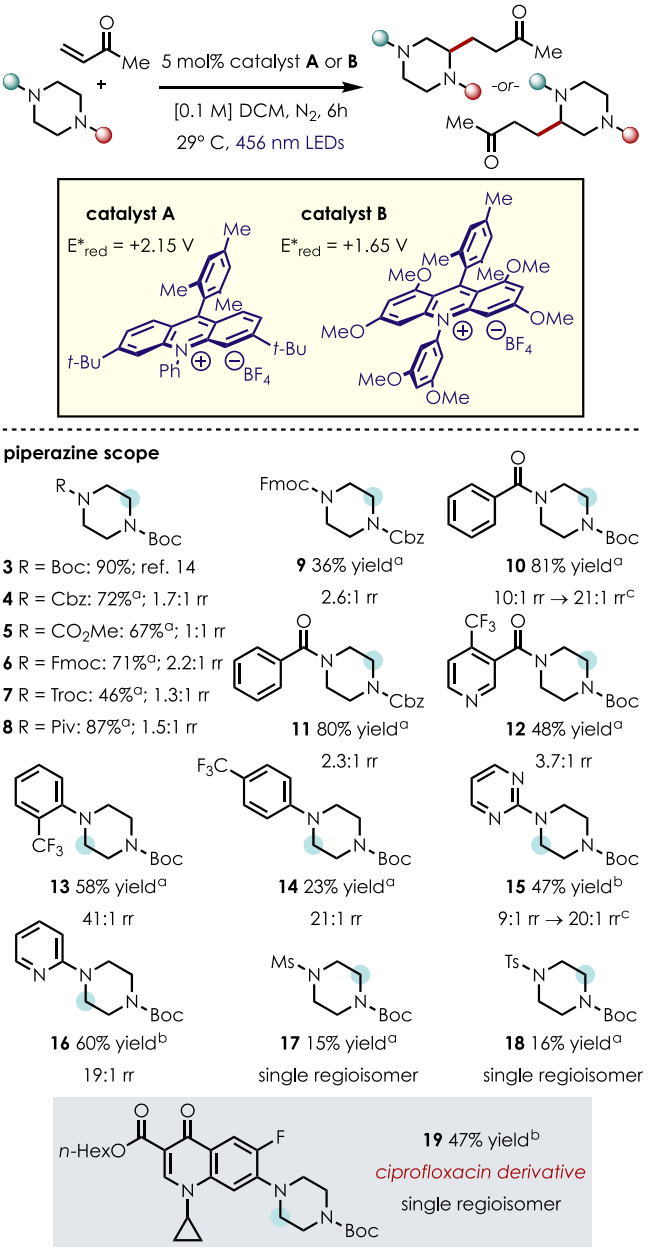
perspective, as the vast array of existing bioactive piperazines could be further functionalized via predictable late-stage modification of the piperazine core.

To develop a synthetically viable strategy as outlined in Figure 2, we believed that sufficient electronic differentiation of the two nitrogen atoms of a piperazine substrate would be necessary for a site-selective reaction to proceed. We hypothesized that a photoinduced electron transfer (PET) event oxidizing a differentially N,N′-disubstituted piperazine substrate would form a nitrogen-centered cation radical at the more electron-rich locus. Single-electron oxidation at the more electron-rich nitrogen center followed by deprotonation and subsequent spin-center shift would yield α-amino radical **1** (Figure 2A). These versatile reactive intermediates have been utilized to introduce varied functionality α to a nitrogen center.[16] Herein,l we describe a site-selective approach to direct C−H alkylation of piperazine compounds through the electronic differentiation of the two nitrogen centers within the heterocycle.

Adapting conditions from work previously developed and disclosed by our lab,[14] we combined the piperazine substrate with an acridinium photocatalyst (**A** or **B**) and the electrophilic coupling partner, methyl vinyl ketone (MVK). Utilizing the conditions displayed in Scheme 1, we were able to establish general reactivity of piperazine substrates by coupling *N,N′*-diBoc-piperazine with MVK to from adduct **3** in excellent yield.[14] While this result showed proof of concept, neither nitrogen center on *N,N′*-diBoc-piperazine could be differentiated from a stereoelectronic perspective, following the alkylation event. This prevents downstream transformations of **3** via the selective deprotection of a single Boc group. Because of this limitation, we sought to apply this method to piperazines bearing differentiated functionality or orthogonal protecting groups on the two nitrogen centers.

To this end, we were intrigued to find that compound **4** could be accessed from *N*-Boc-*N′*-Cbz-piperazine in a 1.7:1 mixture of regioisomers and in good yield. While this example

Scheme 1. Scope of the Site-Selective Piperazine Alkylation Reaction[d]



[a]Catalyst **A**. [b]Catalyst **B**. [c]Reaction performed at 0 °C. [d]Isolated yields and regioselectivities are averages of two trials.

shows only modest selectivity for α-functionalization favoring the Boc-carbamate, the differentiation between two similar carbamate functional groups demonstrates the promising chemoselectivity of this approach.

Further exploration into substituent effects on nitrogen revealed that modest selectivity can be achieved between a number of carbamate functional groups using this method (**4**–**7** and **9**). In addition to carbamates, trimethylacetamide was also tolerated under these conditions to form **8** in a 1.5:1 ratio, again favoring reactivity proximal to the Boc-protected nitrogen. Benzamide derivatives **10**–**12** could also be smoothly converted to the desired alkylation adducts in good isolated yields and excellent regioselectivity in the case of **10**.

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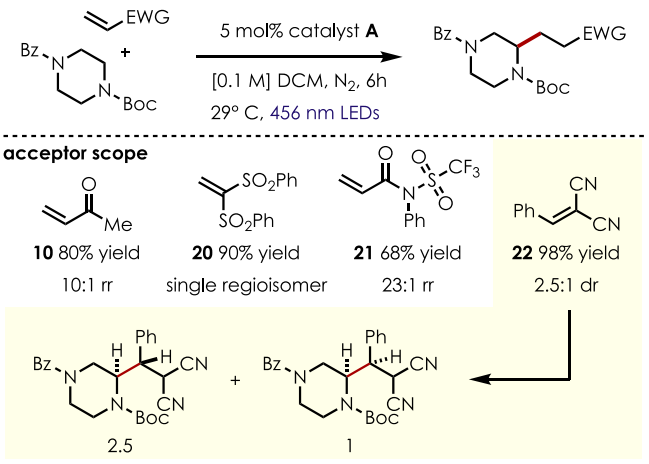
Moreover, **10** could be scaled up from 0.3 to 1.0 mmol without notable changes in yield or rr (see the Supporting Information for details). This ability to electronically differentiate between two common nitrogen protecting groups underscores the utility of this method. Such a protocol allows for a stepwise procedure for accessing synthetically valuable piperazine building blocks.

Next, we sought to probe the compatibility of more electron-rich nitrogen centers compared to those derived from carbamates and amides. It was determined that arylamine derivatives were well-suited for this reaction and that compounds **13**–**16** could be formed with excellent levels of regiocontrol. Interestingly, we observed a reversal in regioselectivity for these substrates with alkylation occurring preferentially proximal to the more electron-rich arylamine. A similar effect is observed for strongly withdrawing sulfonamide protecting groups with alkylation occurring exclusively at the site proximal to the *N*-Boc group, albeit in lower yields (**17** and **18**). Lastly, this method was applied to the late-stage functionalization of a derivative of the commercial antibiotic, ciprofloxacin (**19**), in fair yield and as a single regioisomer. During the development of this procedure, it was discovered that the regioselectivity of alkylation was strongly dependent on reaction temperature. Thus, when the reaction mixture was cooled from 29 to 0 °C, the regioselectivity for this transformation could be enhanced, increasing the rr for **10** from 10:1 to 21:1 and that for **15** from 9:1 to 20:1 (see the Supporting Information for details); these trials did not affect which regioisomer forms as the major product.

In addition to MVK, several other Michael acceptors could be coupled to the piperazine substrates in an analogous fashion. Scheme 2 displays these Michael acceptors, now

Scheme 2. Scope of the Radical Acceptors[a]



[a]Isolated yields and regioselectivities are averages of two trials.

bearing withdrawing groups such as sulfones (**20**), amides (**21**), and nitriles (**22**). Interestingly, acceptors **20**–**22** gave enhanced regioselectivity when compared with that with MVK, with acceptors **20** and **22** giving the desired products in excellent yields and as single regioisomers.

To further understand the driving force behind the site selectivity observed in Schemes 1 and 2, DFT natural population analysis (NPA) was utilized as a means to predict product outcome. To effectively utilize NPA to predict the major product for these reactions, computational analysis was performed to measure the relative electron density at both nitrogen centers in the neutral (q) substrate along with the cation radical intermediate ($q^{\bullet+}$) (see the Supporting Information for details). The site selectivity was then predicted by measuring the change in the NPA values of the individual nitrogen atoms between the neutral species and the corresponding radical cation (Δq), wherein the nitrogen atom that undergoes the most drastic change in electron density was predicted to be the principal site of alkylation.[17,18] Figure 3 illustrates this phenomenon for a set of substrates, and

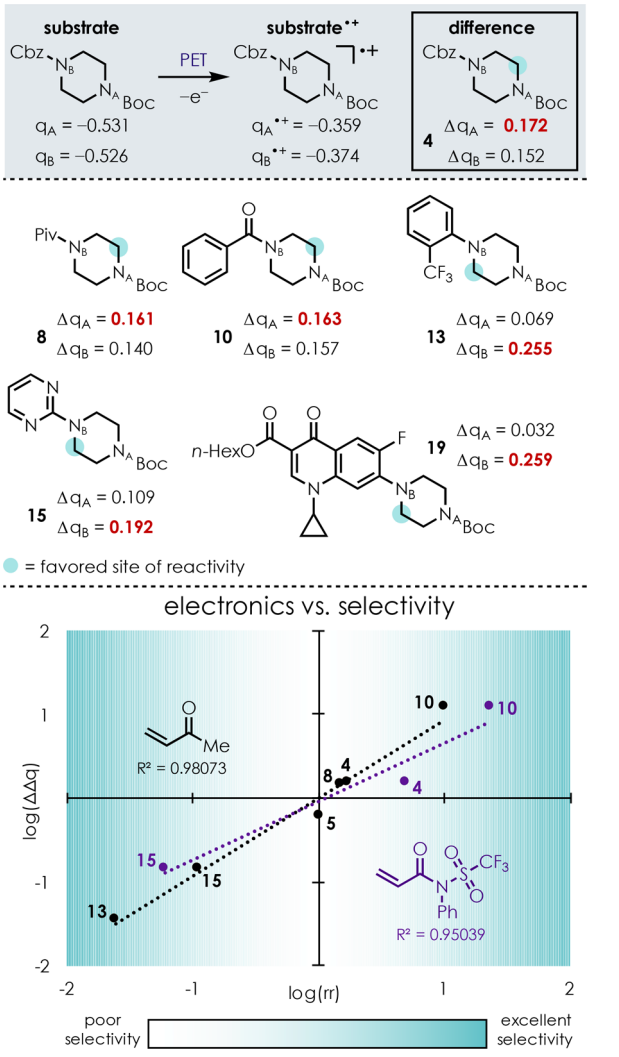


Figure 3. Natural population analysis of selected piperazine substrates with the correlation between piperazine electronics and site selectivity.

in most cases, the major product isomer was successfully predicted using this type of NPA analysis. This predictive model was effective even for piperazines with seemingly electronically indistinguishable groups on nitrogen (**4** and **8**). Additionally, site selectivity could be predicted regardless of the site of alkylation, with accurate predictions for products featuring either proximal (**4** and **8**–**10**) or distal (**13**, **15**, and **19**) functionalization to the *N*-Boc moiety. The sole outliers in this study were compounds **9** and **17**. Computational analysis of $\mathbf{9}^{\bullet+}$ revealed that the majority of charge density was localized on the fluorene moiety of the Fmoc group, rather than the piperazine, leading to product prediction that does not

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correlate with experimental evidence. As for sulfonamide-protected adduct **17**, alkylation adjacent to the sulfonamide is predicted as the major product. We postulate that the α-sulfonamidoyl radical is indeed formed preferentially to the expected α-carbamyl radical; however, due to known decomposition pathways of α-sulfonamidoyl radicals, formation of the predicted C−H alkylation adduct is stymied, resulting in the minor distal alkylation adduct being the only observed product.[19] This would also account for the diminished yields of these substrates.

We expected that our computational results should reflect not only the identity of the major product but also the overall regioselectivity (rr) of the transformation. We were pleased to observe that when the log of the regioisomeric ratio [log(rr)] was plotted against the log of the difference between calculated Δq values [log($\Delta\Delta q$)], a linear relationship was observed (see the Supporting Information for computation details). The graph in Figure 3 shows a plot of this calculated linear relationship relative to an *N*-Boc group at 29 °C. Substrates plotted in the blue portions of the graph exhibit high selectivity under these reaction conditions with compounds on the right favoring functionalization adjacent to *N*-Boc and those to the left favoring alkylation opposite to that group. This relationship suggests that regioselectivity is governed solely by the cation radical character on each nitrogen and has little to do with steric considerations or the pK_a of the proton α to the radical cation. It is worth noting that these calculations predicted that **19** would be functionalized with a 48:1 rr, favoring alkylation adjacent to the *N*-aryl group. For **19**, we were able to detect only a single regioisomer matching the predicted major product.

When utilizing *N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]-acrylamide (**21**) as the radical acceptor, the observed regioselectivities in these reactions also correlated well with calculated Δq values. The differing slope of this line (cf. Figure 3) relative to that of the plot generated using MVK as an acceptor reflects differences in the electronic properties of these two acceptors. In future iterations of this analysis, the inclusion of a second parameter or set of parameters designed to account for Michael acceptor electronics would allow for the unification of these data into a single curve, via multivariate analysis.

Lastly, we sought to explore how preexisting substitution patterns along the piperazine core affect the site selectivity of this process. Compounds **23** and **24** were prepared as single regioisomers and diastereomers, with their structures confirmed by X-ray crystallography (Figure 4A). These crystal structures illustrate the importance of an axial relationship among substituents about the piperazine core in systems with amide and carbamate protecting groups on the nitrogen centers. We posit that the selectivity of these reactions is dictated via a Fürst−Plattner-type transition state in which the preinstalled methyl groups are situated in a pseudoaxial orientation to minimize buildup of $A^{1,3}$ strain with the adjacent carbonyl group (Figure 4B).[14,20,21] Although **24** was formed in only 16% yield, we believe this is in accordance with the results discussed thus far as we would expect selectivity to occur adjacent to the *N*-Boc center; however, if these sites are congested by preexisting functionality, we expect to see poor conversion to an adduct resembling **24**.

In conclusion, we have developed a method for the site-selective C−H alkylation of piperazine compounds, tolerant of a variety of orthogonal and versatile nitrogen protecting groups. This procedure showed a dependence on the reaction temperature where site selectivity could be enhanced by decreasing reaction temperatures. Natural population analysis was also utilized to establish a predictive model for site selectivity, complementing experimental results. It is our hope that the synthetic utility of this transformation eases the access to more structurally diverse piperazine compounds.

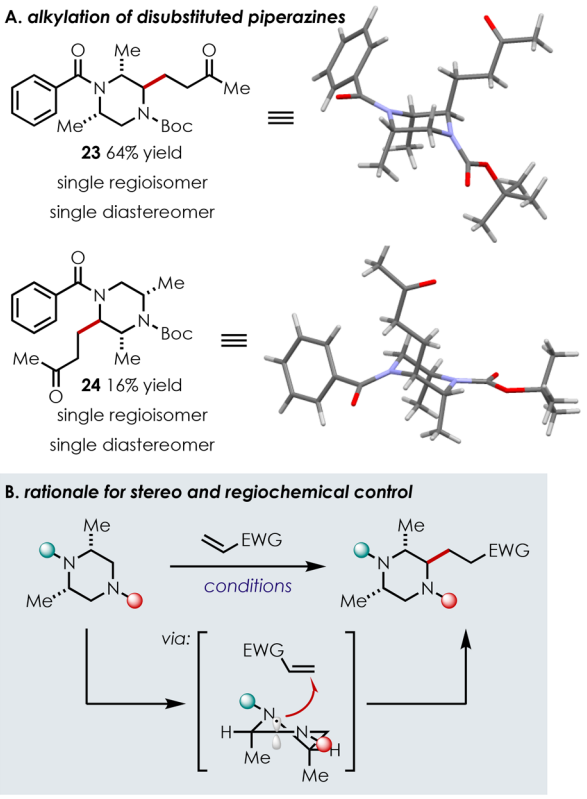

Figure 4. Selectivity patterns in alkylated piperazine substrates. Isolated yields and regioselectivities are averages of two trials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04456.

Experimental procedures, X-ray data, and supporting ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1957034−1957036 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nicewicz@.unc.edu.

ORCID

Nicole C. Goodwin: 0000-0002-6093-7175

David A. Nicewicz: 0000-0003-1199-9879

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Notes

The authors declare no competing financial interest.

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